Original Article

Efficacy and safety of first-generation epidermal growth factor receptor tyrosine kinase inhibitors in retreatment of patients without T790M

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Background: Patients receiving first-line epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) and undergoing second and/or third-line cytotoxic chemotherapy may experience regrowth of EGFR (+) clones. Retreatment with EGFR TKIs can provide antitumor effects and potentially induce T790M-positive conversion. This study evaluated the efficacy, safety, and T790M (+) conversion rates in patients without T790M mutation at the second biopsy retreated with first-generation EGFR TKIs as third-line or subsequent therapy.

Methods: This open-label, multi-center, prospective phase II trial (NCT03382795) enrolled patients with non-small cell lung cancer (NSCLC) previously treated with first- or second-generation EGFR TKIs and cytotoxic chemotherapy They were retreated with gefitinib or erlotinib. Key endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety.

Results: Among 63 patients (34 on gefitinib, 29 on erlotinib), ORR was 14.3%. Median PFS was 2.2 months, and median OS was 8.6 months. Adverse events occurred in 82.5% of patients, primarily grade ≤2. The T790M conversion rate was 31.7% and was significantly associated with prior EGFR TKI exposure duration (P=0.047). Patients with T790M conversion had a median OS of 29.3 months, significantly (P<0.001) longer than the median OS of 6.0 months for non-converters. Next-generation sequencing (NGS) of pre-retreatment blood samples identified additional T790M mutations (20.8%) undetected by conventional testing. Low TP53 expression showed a non-significant trend toward higher tendency T790M conversion (66.7% *vs.* 30.8%, P=0.32).

Conclusions: EGFR retreatment induced T790M conversion in 32% of cases, enabling third-generation

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EGFR TKIs, leading to a substantial improvement in median OS. Blood-based NGS identified additional T790M mutations, undetected by routine polymerase chain reaction (PCR). EGFR TKI retreatment with blood-based NGS may enhance patient prognosis by identifying additional T790M positive mutations.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor tyrosine kinase inhibitor retreatment (EGFR TKI retreatment); T790M mutation

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Introduction

Background

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide. The prognosis for advanced or metastatic NSCLC remains poor, with a 5-year survival rate ranging from 2% to 10%. The introduction of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in the early 2000s has significantly improved outcomes for patients with EGFR-mutant adenocarcinoma, extending median overall survival (OS) from approximately 10 to 36 months (1).

Highlight box

Key findings
- Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) retreatment with blood-based next-generation sequencing (NGS) may enhance patient prognosis.
- Blood NGS test could identify T790M mutations in patients whose mutations were not detected by the conventional EGFR test commonly used in clinical practice.
- No significant differences in outcomes or stability existed between groups receiving different EGFR TKIs or having different EGFR mutation status.

What is known and what is new?
- Sequential treatment using 3rd generation EGFR TKIs after first/second-generation usage remains one of the treatment options for patients with EGFR mutation.
- We assessed the efficacy and safety of EGFR TKI retreatment, emphasizing T790M positive conversion.

What is the implication, and what should change now?
- EGFR TKI retreatment may become one of several treatment options in the future.

Rationale and knowledge gap

Clinical efficacies of first and second-generation EGFR TKIs is limited by acquired resistance, which typically emerges 9 to 11 months after initiating treatment with EGFR TKIs (2,3). A primary mechanism of resistance is the development of T790M mutation (4,5). Various clinical trials have evaluated third-generation EGFR TKIs, designed to selectively target T790M, presenting a promising avenue for overcoming acquired resistance (6,7).

Third-generation EGFR TKIs are the standard treatment for NSCLC; however, sequential treatment using third-generation EGFR TKIs following first/second-generation therapy remains an option for patients with EGFR mutations in many countries. In these patients, if T790M is not detected after using first-line EGFR TKIs, cytotoxic chemotherapy is the standard treatment. However, challenges exist in defining optimal therapeutic strategies for T790M negative patients and those with unknown resistance mechanisms. Clinical studies on EGFR TKIs retreatment for patients who initially responded but later developed acquired resistance after undergoing cytotoxic chemotherapy have demonstrated a response rate of approximately 20%, a progression-free survival (PFS) of approximately 4 months, and an OS of 12 months (8-10).

Previous studies on EGFR TKI retreatment often lacked accurate evaluation due to the absence of re-EGFR mutation testing, making it difficult to assess the likelihood of T790M (+) conversion and accurately respond to EGFR TKI retreatment. Excluding T790M positive patients from re-biopsy and selectively treating those with other sensitizing EGFR mutations (+) might improve response rates and PFS compared to reports of previous clinical studies.

Objective

This prospective study aimed to determine clinical efficacy, side effects, and factors related to T790M induction in T790M-negative patients retreated with first-generation EGFR TKIs. The primary objective was to evaluate the clinical utility and safety of EGFR TKI retreatment. Additionally, the study sought to explore the incidence of T790M mutations upon re-biopsy at the point of progression after EGFR TKI retreatment and to assess the potential switch to third-generation EGFR TKI therapy in such patients. We present this article in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-36/rc).

Methods

This clinical trial (clinical trial number: NCT03382795) was an open-label, multi-center, prospective phase II study designed to assess the efficacy and safety of gefitinib or erlotinib in patients who previously responded to EGFR TKIs and later tested negative for T790M but positive for other sensitizing EGFR mutations using tissue or blood samples following cytotoxic chemotherapy (Figure S1). The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee for Clinical Research of the Korea University Guro Hospital (IRB No. 2017GR0230) and informed consent was taken from all the patients. All patients enrolled in this study were Korean and all participating hospitals/institutions were informed and agreed the study.

Study design

This study enrolled patients aged 19 years or more with non-squamous NSCLC who underwent first-line treatment with first-generation or second-generation EGFR TKIs (Appendix 1). Patients who progressed after cytotoxic chemotherapy administered as second-line treatment were eligible for this study. Re-biopsy, either tissue or blood-based, was performed to confirm the absence of the T790M mutation and the presence of other sensitizing EGFR mutations (E19Del, L858R, L861Q, and G719X). Enrolled patients switched to a different first-generation EGFR TKI (gefitinib 250 mg or erlotinib 150 mg) during subsequent retreatment. Patients had initially received erlotinib or afatinib as first-line treatment were allocated to the gefitinib retreatment group, while those who had initially been treated with gefitinib were assigned to an erlotinib retreatment group. Each treatment cycle was defined as 28 days, with cycles repeating for patients until they experienced disease progression or intolerable toxicity. A follow-up period of approximately 2 years was planned, starting from the registration of the last subject. The primary endpoint was the objective response rate (ORR) following drug administration. Secondary endpoints included PFS, OS, and safety post-drug administration.

Additionally, a biomarker study was conducted using samples from two distinct time points to evaluate T790M (+) conversion. At the first time point, blood biopsy specimens were obtained after EGFR retreatment. At the second time point, blood samples were collected before EGFR retreatment for next-generation sequencing (NGS) for 24 patients. Patients who exhibited more than the median PFS with specimens adequately preserved were selected for NGS analysis.

Statistical analysis

Data were analyzed using SPSS 20 software (SPSS for Windows, SPSS Inc., Chicago, IL, USA). Categorical variables were reported as numbers (%), and continuous variables were presented as mean ± standard deviation. Patients were categorized into two groups based on the EGFR TKI drug used for retreatment and EGFR mutation status for prognosis evaluation. Continuous variables were analyzed using Student's *t*-test or Mann-Whitney test, while categorical variables were analyzed using Chi-square test or Fisher's exact test. The latter was used when the expected number of events was less than five.

PFS was calculated as the period from starting the EGFR retreatment until the first progression evaluated by chest computed tomography (CT) or positron emission tomography (PET)/CT. OS was calculated as the period from the start of EGFR retreatment to the date of death from any cause. The Kaplan-Meier method and log-rank test were utilized to analyze PFS and OS. A P value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics and previous treatment history

Eight academic hospital sites participated in this clinical trial, enrolling a total of 63 patients, with 34 in the gefitinib group and 29 in the erlotinib group (*Table 1*). In gefitinib group (n=34), 23 had received afatinib as first-line therapy,

Table 1 Baseline characteristics and previous treatment history

Variables	Total patients (n=63)	Gefitinib group (n=34)	Erlotinib group (n=29)	P
Gender				0.01
Male	26 (41.3)	19 (55.9)	7 (24.1)	
Female	37 (58.7)	15 (44.1)	22 (75.9)	
Age (years)	64.7±10.9	64.2±10.4	65.3±11.6	0.70
Smoking history				0.32
Never smoker	42 (66.7)	20 (58.8)	22 (75.9)	
Ex-smoker	19 (30.2)	13 (38.2)	6 (20.7)	
Current smoker	2 (3.2)	1 (2.9)	1 (3.4)	
Baseline stage				>0.99
III	2 (3.25)	1 (2.9)	1 (3.4)	
IV	61 (96.8)	33 (97.1)	28 (96.6)	
Histologic type				>0.99
Adenocarcinoma	62 (98.4)	33 (97.1)	29 (100.0)	
Adenosquamous carcinoma	1 (1.6)	1 (2.9)	0 (0.0)	
Baseline EGFR mutation type				0.12
E19del	37 (58.7)	23 (67.6)	14 (48.3)	
L858R	25 (39.7)	10 (29.4)	15 (51.7)	
G719X	1 (1.6)	1 (2.9)	0 (0.0)	
Previous treatment line				0.054
2	25 (39.7)	14 (41.2)	11 (37.9)	
3	27 (42.9)	14 (41.2)	13 (44.8)	
4	6 (9.5)	1 (2.9)	5 (17.2)	
5	5 (7.9)	5 (14.7)	0 (0.0)	
Duration of initial EGFR TKI usage (days)	405.6±278.7	390.4±210.3	423.4±345.3	0.38
Time from last use of EGFR TKI to use of EGFR TKI again (days)	358.7±301.1	345.7±310.4	374.0±294.5	0.21
Presence of platinum doublet therapy	48 (76.2)	27 (79.4)	21 (72.4)	0.52
Comorbidity				
Hypertension	23 (36.5)	11 (32.4)	12 (41.4)	0.46
Diabetes mellitus	15 (23.8)	10 (29.4)	5 (17.2)	0.23
COPD	4 (6.3)	4 (11.8)	0 (0.0)	0.056

Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as numerical values and percentages. COPD, chronic obstructive pulmonary disease; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

and 11 had received erlotinib as first-line therapy. The majority of patients were females (58.7%) and non-smokers (66.7%). All patients except for two were in stage IV, and all but one were diagnosed with adenosquamous carcinoma. The gefitinib and erlotinib groups showed no significant differences in baseline characteristics, except that the gefitinib group had a higher proportion of males (P=0.01).

Regarding previous treatment, the majority of patients exhibited E19del (58.7%) and L858R (39.7%) mutations. Most (82.6%) patients received EGFR TKI retreatment as

Table 2 Response to retreatment

Variables	Total patients (n=63)	Gefitinib group (n=34)	Erlotinib group (n=29)	P
RECIST				0.21
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	
Partial response	9 (14.3)	3 (8.8)	6 (20.7)	
Stable disease	24 (38.1)	12 (35.3)	12 (41.4)	
Progressive disease	21 (33.3)	15 (44.1)	6 (20.7)	
Not evaluable	9 (14.3)	4 (11.8)	5 (17.2)	
ORR	9 (14.3)	3 (8.8)	6 (20.7)	0.28
DCR	33 (52.4)	15 (44.1)	18 (62.1)	0.16

Categorical variables are expressed as numerical values and percentages. DCR, disease control rate; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

the third- or fourth-line of treatment. The average duration of first-line EGFR TKI use was 13.5±9.3 months, and the average time from the last EGFR TKI use to EGFR TKI retreatment was 12.0±10.0 months. All enrolled patients had received at least one cycle of cytotoxic chemotherapy. Among them, 32 patients (49.2%) received only one type of cytotoxic chemotherapy, while 33 patients (50.8%) received two or more types of cytotoxic chemotherapy. Most (76.2%) patients received platinum doublet therapy through cytotoxic chemotherapy, with 81.0% of patients using pemetrexed.

Retreatment response

The ORR, the primary endpoint, was observed in 9 (14.3%) patients (*Table 2*). The disease control rate (DCR) was 52.4% (33 patients), with no patient achieving a complete response. The median PFS for the total patient cohort was 2.2 [95% confidence interval (CI): 1.4–3.0] months, and the median OS was 8.6 (95% CI: 6.3–10.8) months (*Figure 1A*,*1B*). Subgroup analyses comparing gefitinib with erlotinib and E19del with L858R mutations revealed no significant difference in median PFS or OS. The prognosis was consistent regardless of the drug (gefitinib *vs.* erlotinib) administered or the EGFR mutation status (E19del *vs.* L858R) (Figure S2A-S2D). The median PFS in the gefitinib group was 1.8 (95% CI: 2.0–1.9) months, and the median PFS in the erlotinib group was 3.0 (95% CI: 1.2–4.9) months, with no statistically significant difference (P=0.10). The median PFS in the E19del group was 2.3 (95% CI: 0.4–4.2) months, and the median PFS in the L858R group was 2.1 (95% CI: 1.7–2.4) months, showing no statistically significant difference (P=0.39).

Analysis of T790M (+) conversion using samples after retreatment

Among the 63 patients, 60 underwent additional tissue or blood biopsy after retreatment to confirm T790M (+) conversion. Among the 60 patients, 23 (38.3%) were assessed for T790M conversion using both tissue and blood samples, 20 (33.3%) using only tissue, 16 (26.7%) using only blood, and 1 (1.7%) using both blood and pleural effusion. T790M (+) conversion was confirmed in 20 of these 60 patients. Among these 20 patients, the T790M mutation was detected in 11 through blood, 8 through tissue, and 1 through pleural fluid.

Among the 20 patients with confirmed T790M (+) conversion, third-generation TKIs were administered to all patients except one, with 17 patients receiving osimertinib and two receiving lazertinib. PFS and OS were not significantly different between the two drugs (osimertinib *vs.* lazertinib), with P of 0.88 and 0.45, respectively. The T790M (+) conversion group treated with third-generation EGFR TKIs, exhibited a substantially longer median OS of 29.3 (95% CI: 11.3–47.3) months compared to the T790M (–) group, which had a median OS of 5.0 (95% CI: 2.3–7.7) months (P<0.001) (*Figure 2*).

Univariate analysis was conducted on T790M (+) conversion. Baseline characteristics, including histologic type, baseline EGFR mutation type, and cytotoxic treatment, showed no significant differences between patients with and without T790M (+) conversion (Table S1). The duration of exposure to EGFR TKI emerged as the

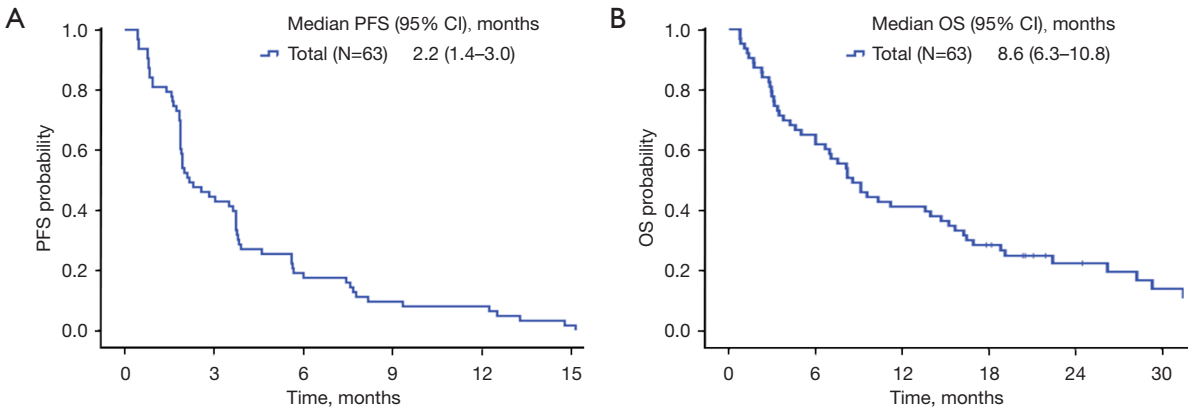

Figure 1 Median PFS (A) and median OS (B) of total patients. CI, confidence interval; OS, overall survival; PFS, progression-free survival.

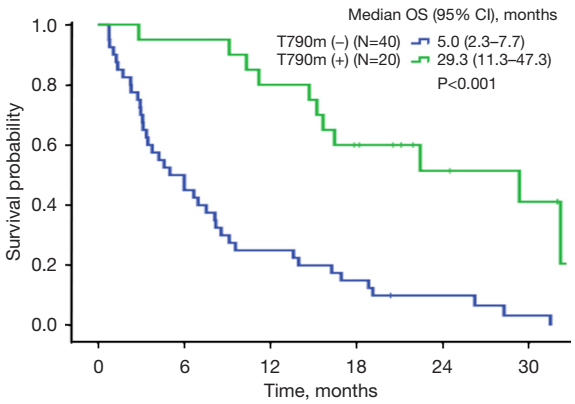

Figure 2 OS based on presence of T790M mutation. CI, confidence interval; OS, overall survival.

primary factor inducing T790M (+) conversion (*Table 3*). Statistical analysis indicated that the duration of initial EGFR TKI usage, retreatment duration with EGFR TKI, and combined duration were significantly longer in the T790M (+) conversion group than in the T790M (–) group (P were 0.03, 0.03, and 0.047, respectively). Moreover, all patients in the T790M (+) group had at least 6 months of first-line EGFR TKI usage (P=0.048).

Adverse events (AEs)

AEs were observed in 52 (82.5%) patients. Most of these events were grade 2 or lower, with 14 (22.2%) patients experiencing grade 3 or higher AEs. The most common side effect was gastrointestinal disorders (23.5%) in the gefitinib group, while skin and subcutaneous tissue disorders (55.2%) were the most common side effects in the erlotinib group. Apart from the higher incidence of skin and subcutaneous tissue disorders in the erlotinib group, no significant differences were noted between the two groups. Dose reduction due to side effects occurred in 11 (17.5%) patients. The AE pattern observed in this study was similar to that reported in previous studies of other EGFR TKIs (*Table 4*).

NGS analysis of T790M (+) conversion using pre-retreatment samples

NGS testing was performed using pre-retreatment blood samples from 24 of the 63 patients enrolled. NGS identified five patients with T790M mutation previously undetected by conventional EGFR mutation testing on tissue or blood biopsy at retreatment trial enrollment. Subsequent post-retreatment samples confirmed T790M positivity in all five patients with T790M mutation identified by NGS. The five T790M-positive patients had a significantly shorter median PFS of 1.9 (95% CI: 1.9–2.0) months during retreatment compared to a median PFS of 4.6 (95% CI: 1.9–7.3) months in the 19 patients without the T790M mutation (P=0.002) (*Figure 3*). Additionally, the five patients with T790M mutations detected by NGS had a median OS of 20.2 (95% CI: 8.0–32.5) months, which was similar to the median OS of 27.3 (95% CI: 19.3–35.2) months observed in the T790M-positive group identified after retreatment. However, their OS differed from the median OS of 8.5 (95% CI: 5.9–11.2) months in the T790M-negative group (P<0.001). Consequently, these 5 (20.8%) patients were identified as T790M positive through NGS using blood samples, despite being missed by conventional tests.

Among the remaining 19 patients, 13 tested positive

Table 3 Analysis of factors related to T790M (+) conversion

Variables	Total patients (n=60)	T790M positive (n=20)	T790M negative (n=40)	P
Data on first-line EGFR TKI treatment				
Duration of first EGFR TKI usage (days)	408.5±283.2	488.2±345.9	368.7±241.1	0.03
First-line EGFR TKI used for more than 6 months	53 (88.3)	20 (100.0)	33 (82.5)	0.048
First-line EGFR TKI used for more than 1 year	28 (46.7)	12 (60.0)	16 (40.0)	0.14
Time from last EGFR TKI use to subsequent EGFR TKI use (days)	355.0±305.0	301.3±271.5	381.9±320.1	0.13
PFS of retreatment with EGFR TKI (days)	118.6±110.1	129.5±88.9	113.2±120.0	0.03
Total duration of EGFR use (duration of first EGFR TKI use + PFS) (days)	527.1±320.7	617.7±392.2	481.9±272.6	0.047

Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as numerical values and percentages. EGFR, epidermal growth factor receptor; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Table 4 Treatment-related AEs

AEs	Total patients (n=63)	Gefitinib group (n=34)	Erlotinib group (n=29)	P
AE any cause				
Any AE	52 (82.5)	27 (79.4)	25 (86.2)	0.49
Any AE grade 1 or 2	38 (60.3)	20 (58.8)	18 (62.1)	0.80
Any AE grade 3 or higher	14 (22.2)	7 (20.6)	7 (24.1)	0.74
Dose reduction	11 (17.5)	3 (8.8)	8 (27.6)	0.051
Gastrointestinal disorders	28 (44.4)	13 (38.2)	15 (51.7)	0.21
Skin and subcutaneous tissue disorders	24 (38.1)	8 (23.5)	16 (55.2)	0.01
Respiratory, thoracic, and mediastinal disorders	16 (25.4)	10 (29.4)	6 (20.7)	0.31
Musculoskeletal and connective tissue disorders	16 (25.4)	9 (26.5)	7 (24.1)	0.53
General disorders and administration site conditions	12 (19.0)	8 (23.5)	4 (13.8)	0.26
Infections and infestations	11 (17.5)	5 (14.7)	6 (20.7)	0.38
Metabolism and nutrition disorders	7 (11.1)	3 (8.8)	4 (13.8)	0.41
Nervous system disorders	6 (9.5)	2 (5.9)	4 (13.8)	0.26
Hepatobiliary disorders	6 (9.5)	3 (8.8)	3 (10.3)	0.58
Blood and lymphatic system disorders	3 (4.8)	2 (5.9)	1 (3.4)	0.56
Psychiatric disorders	3 (4.8)	2 (5.9)	1 (3.4)	0.56
Eye disorders	2 (3.2)	2 (5.9)	0 (0.0)	0.29
Cardiac disorders	1 (1.6)	1 (2.9)	0 (0.0)	0.54

Categorical variables are expressed as numerical values and percentages. AE, adverse event.

for T790M (+) in post-retreatment samples. Due to an insufficient number of samples, it was impossible to identify statistically significant genes related to T790M (+) conversion in the analysis of these 13 T790M (+) and 6 T790M (–) patients. The prevalence of the *TP53* gene in the T790M-positive group (30.8%) tended to be lower than that of the T790M-negative group (66.7%), although their difference was not statistically significant (P=0.32).

Analysis of T790M conversion rates based on initial EGFR TKI

There is interest in whether the use of first-generation EGFR TKIs (gefitinib or erlotinib) *vs.* second-generation EGFR TKIs (afatinib) as first-line therapy is associated with the T790M conversion rate. In our study, we reassessed T790M status after EGFR TKI retreatment in 60 patients and observed T790M conversion in 20 of them. Among these 20 patients, five had already been identified as T790M-positive through NGS of blood samples prior to EGFR TKI retreatment. Therefore, we analyzed the difference in T790M conversion rates between first- and second-generation EGFR TKIs in the entire cohort of 60 patients and in the subgroup of 55 patients, excluding the five who were pre-identified as T790M-positive. Among the 60 patients, 38 had received first-generation EGFR TKIs (gefitinib or erlotinib), and 14 of them (36.8%) exhibited T790M conversion. In contrast, among the 22 patients treated with the second-generation EGFR TKI afatinib, 6 (27.3%) showed T790M conversion, with no statistically significant difference between the groups (P=0.45). In the subgroup analysis of 55 patients (excluding the five who were identified by blood NGS as T790M-positive), 36 had been treated with first-generation EGFR TKIs, and 12 of them (33.3%) exhibited T790M conversion. Meanwhile, among the 19 patients treated with afatinib, 3 (15.8%) demonstrated T790M conversion, again showing no statistically significant difference (P=0.17). Although neither comparison reached statistical significance, the observation that T790M conversion occurred approximately 10–15% more frequently in patients treated with first-generation EGFR TKIs raises the possibility that a significant difference might emerge with a larger patient cohort.

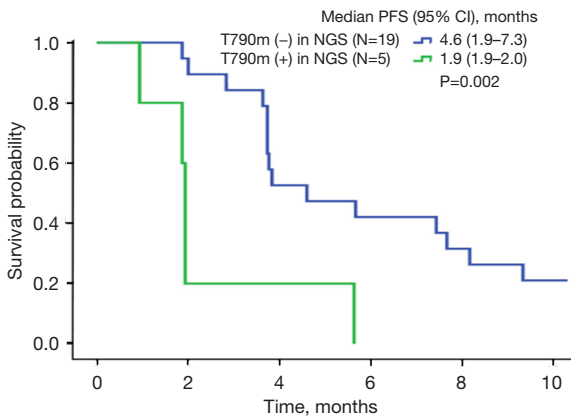

Figure 3 NGS identified T790M mutations previously undetected by conventional EGFR mutation testing on tissue or blood biopsies at the time of retreatment trial enrollment, or non-identified T790M mutations, and their impact on PFS. CI, confidence interval; EGFR, epidermal growth factor receptor; NGS, next-generation sequencing; PFS, progression-free survival.

Discussion

Key findings

This study represents the first prospective clinical trial to evaluate the efficacy and safety of EGFR TKIs retreatment, along with an analysis of T790M (+) conversion by retreatment. Two hypotheses have been proposed to explain the efficacy and feasibility of EGFR retreatment (*Figure 4*). First, EGFR-positive clones initially suppressed by first-

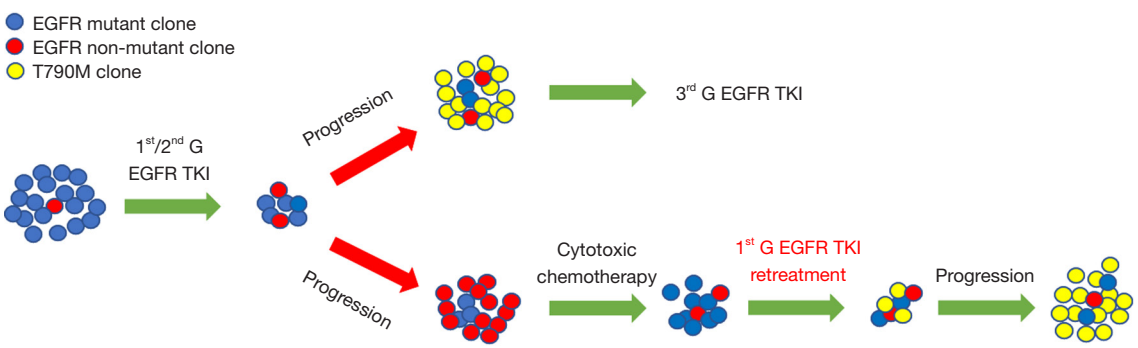

Figure 4 Study hypothesis. Hypothesis 1: after cytotoxic chemotherapy, the non-mutant EGFR clone (red dot) may decrease, while the mutant EGFR clone (blue dot) could regrow. Hypothesis 2: following EGFR retreatment, a T790M-positive clone (yellow dot) not observed previously may emerge. EGFR, epidermal growth factor receptor; G, generation; TKI, tyrosine kinase inhibitor.

line EGFR TKIs might proliferate again during cytotoxic chemotherapy. Second, increasing the duration and exposure to EGFR TKIs could cause T790M (+) conversion in previously undetected T790M mutations. In our study, the ORR was 14.3%, with a median PFS of 2.2 months and a median OS of 8.6 months. AEs occurred in 82.5% of patients; most were grade 2 or lower. There were no significant serious complications related to drug use. There were no significant differences in outcomes or stability between groups receiving different EGFR TKIs or having different EGFR mutation status. EGFR retreatment induced a 31.7% (20/63) T790M (+) conversion. The T790M (+) conversion group (n=19) responded to retreatment and subsequently received third-generation EGFR TKIs, showing a significantly favorable prognosis with a median OS of 29.3 months. The key factor influencing T790M (+) conversion was the duration of EGFR TKI exposure, with both durations of first-line EGFR TKI use and retreatment EGFR TKI use showing statistically significant results. In addition, we conducted NGS testing on blood samples obtained prior to retreatment from 24 patients. Through this analysis, we observed that the blood NGS test could identify T790M mutations in 20.8% (5/24) of patients whose mutations were not detected by the conventional EGFR test commonly used in clinical practice. Although no statistically significant differences were observed, we noted that T790M (+) conversion tended to be induced more in the group with fewer *TP53* gene mutations. This underscores the potential of blood NGS testing to uncover additional T790M mutations, suggesting a possible association between T790M conversion and the *TP53* gene.

Strengths and limitations

This study has some limitations, including its small sample size and varying methods of EGFR testing. Owing to the limited availability of stored specimens, NGS was conducted for 24 individuals only. Moreover, the high sensitivity of NGS facilitated the identification of an additional T790M (+) in five patients, restricting gene comparative analysis to just 19 individuals. Various samples, including tissue, blood, and pleural fluid, were employed for post-retreatment T790M confirmation. Specifically, among the 60 patients, 17 patients did not undergo tissue analysis and were only evaluated for T790M in blood samples. Since genetic analysis between liquid biopsy and the main progression tissue lesion may differ, our study has certain limitations. However, this was necessitated by worsening patient conditions from repeated cancer treatments and risks associated with tissue biopsies. Despite these challenges, our study successfully highlighted the clinical utility of liquid biopsies by confirming a high likelihood of T790M (+) conversion and contributing positively to patient prognosis (11).

Comparison with similar research

Confirming T790M and subsequently using third-generation EGFR TKIs can significantly improve the prognosis of patients (12,13). Among various factors associated with the detection of T790M after using first or second-generation EGFR TKIs, the duration of EGFR TKI exposure is the most crucial. Numerous studies have suggested the potential presence of T790M in patients who have been exposed to first-line EGFR TKIs for a duration exceeding 10–12 months (14-17). Other presumed minor factors include brain metastasis and retroperitoneal lymph node involvement (14,16). Evidence suggests that T790M is more frequently confirmed when there is local progression rather than primary site progression (18). Accordingly, it might be beneficial to consider metastatic sites during re-biopsy. EGFR genetic analyses have suggested a higher incidence of T790M (+) with 19 del than L858R (17,18). Additionally, an association between E746-A750 mutation, a subtype within the 19 del, and the presence of T790M has been proposed (17). In a study from Japan, 20 patients continued using EGFR TKIs despite experiencing progression while on first- or second-generation EGFR TKIs (19). At the point of progression, T790M was not detected in these patients. However, after further use of EGFR TKIs, T790M was confirmed in 11 patients. Thus, suggesting that continued use of EGFR TKIs, including retreatment, may lead to increased T790M (+) conversions.

Explanations of findings

To utilize third-generation EGFR TKIs, T790M detection is essential. Various testing methods, including tissue biopsy (from either the primary cancer lesion or a metastatic site) and plasma analysis using droplet digital polymerase chain reaction (ddPCR) and NGS have been reported. Clinical practice faces limitations due to factors such as patient condition, risks of tissue biopsy, and costs. In our study, although initial tissue biopsies were negative, five T790M (+) patients were identified through subsequent NGS testing of plasma samples. In a meta-analysis of plasma-based

EGFR-T790M mutation testing using ctDNA, the pooled sensitivity was 0.67 (95% CI: 0.64–0.70) and the pooled specificity was 0.80 (95% CI: 0.77–0.83) (20). Compared to tissue-based testing, plasma-based ddPCR identified an additional 10–40% of T790M (+) cases (21,22). NGS demonstrated similar or superior sensitivity to ddPCR (21,23). This underscores the necessity for vigorous efforts to explore T790M with an array of tools based on each patient's clinical scenario.

Conclusions

We assessed the efficacy and safety of EGFR TKI retreatment, emphasizing T790M positive conversion. The ORR was 14.3%, with a median PFS of 2.2 months and a median OS of 8.6 months. AEs occurred in 82.5% of patients. They were primarily of grade 2 or lower, showing no serious drug-related complications. EGFR retreatment induced a significant T790M (+) conversion rate of 31.7% (20/63). The duration of EGFR TKI exposure was identified as a crucial factor influencing this conversion. Our investigation using NGS testing on blood samples identified T790M mutations in 20.8% of patients previously undetected by conventional EGFR tests. While no statistically significant differences were observed, a tendency for T790M (+) conversions to occur more frequently in patients with fewer *TP53* gene mutations was noted.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee for Clinical Research of the Korea University Guro Hospital (IRB No. 2017GR0230) and informed consent was taken from all the patients. All patients enrolled in this study were Korean and all participating hospitals/institutions were informed and agreed the study.

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